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(19)(CA) APPLICATION FOR CANADIAN PATENT (12)

(54) Labeled Chemotactic Peptides to Image Focal Sites of Infection or Inflammation

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ABSTRACT OF THE DISCLOSURE

The invention relates to a method of detecting a site of infection or inflammation, and a method for treating such infection or inflammation, in an individual by administering to the individual a diagnostically or therapeutically effective amount of detectably labeled, or therapeutically-conjugated, chemotactic peptide which accumulates substantially at the infected or inflamed site, said chemotactic peptide having the general structure

N - X - Y - Leu - Phe - Z - W

Where: X = Formyl for agonists
- A more bulky group such as t - Boc for antagonist.

Y = Met or Nle.

Z*= is a spacer sequence such as Gly - Gly - Gly

W*= is a labeling or attachment substituent, i.e.,
N-epsilon (DTPA) Lys - putrsine for labeling.
- OSU (SO_3) for attachment to a high molecular weight carrier

*At the Z and W positions either D or L amino acids can be used.

TITLE OF THE INVENTION

LABELED CHEMOTACTIC PEPTIDES TO IMAGE FOCAL SITES OF INFECTION OR INFLAMMATION

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

This invention is directed to methods of diagnosing and treating sites of infection and inflammation in an individual.

DESCRIPTION OF THE BACKGROUND ART

Inflammation occurs in response to various forms of tissue damage. This tissue damage can result from microbial invasion, autoimmune processes, tissue or organ allograft rejection, or such injurious external influences as heat, cold, radiant energy, electrical or chemical stimuli, or mechanical trauma. Whatever the cause or bodily site, the ensuing inflammatory response is quite similar, consisting of a complicated set of functional and cellular adjustments, involving the changes in microcirculation, movement of fluids, and influx and activation of inflammatory cells (leukocytes). This response pattern constitutes an important part of innate host defense mechanisms against infection, and although it carries the "cost" of additional tissue damage resulting from the inflammatory process itself, it ultimately promotes the subsequent repair process.

Upon microbial infection, or following certain forms of tissue damage, soluble chemical substances are elaborated which initiate

the inflammatory response cascade, consisting of a complex series of event.

Blood flow in the inflammatory site is increased, and in response to increased capillary permeability, there is an efflux of fluid from the blood. This localized exudation of fluid at the site of injury includes plasma proteins that normally leave the capillaries at a relatively low rate. Leukocytes also leave the capillaries into the inflammation site, both by passive and active processes. The inflammatory cellular exudate initially consists primarily of polymorphonuclear (PMN) leukocytes (also termed neutrophils or granulocytes). Subsequently, monocytes, lymphocytes, and plasma cells can be found in the inflammatory infiltrate. These leukocytes produce a variety of mediators that control the extent and duration of the inflammatory response, and bear on their surface a variety of receptors which can bind and respond to the chemical mediators and other proteins present in the inflammatory fluid. Such receptor-mediator interactions are important in controlling leukocyte function within the inflammatory site.

One such class of inflammatory mediators are the chemotactic factors, also called chemoattractants, which have the capacity to induce the directed migration of PMNs, and macrophages (see for general review and discussion: Roitt, I., et al., IMMUNOLOGY, Gower Medical Pub., London, 1985). Many species of bacteria can produce one or more types of chemotactic molecules, either small peptides, larger proteins or lipids (Klein, J., IMMUNOLOGY: THE SCIENCE OF SELF-NONSELF DISCRIMINATION, Wiley Interscience, NY, 1982).

For example, E. coli bacteria are known to produce potent chemotactic molecules which have as their active components small, heterogeneous peptides with blocked amino groups. Such peptides have been synthesized and shown to be potent chemoattractants for PMNs. The best known of these chemotactic peptides are N-formyl-methionyl-leucyl-phenylalanine (f-Met-Leu-Phe) and some related tetrapeptides (Schiffman, E., et al., Proc. Natl. Acad. Sci. USA 72:1059-1062 (1975); Schiffman et al., U.S. Patent 4,427,660 (1984)). Structure-function studies of these peptides suggested the presence of stereo-specific receptors on the surface of target cells

(Becker, E.L., Am. J. Pathol. 85:385-394 (1976)); such receptors were subsequently detected using radiolabeled formyl peptides as ligands (Williams, L.T., et al., Proc. Natl. Acad. Sci. USA 74:1204-1208 (1977)).

Subsequently, a chemotactic peptide was synthesized with the structure N-Formyl-Nle-Leu-Phe-Nle-Tyr-Lys, which could be labeled to a higher specific radioactivity with ^{125}I at the Tyr residue, and was shown to bind strongly to receptors on human neutrophils (Niedel, J., et al., J. Biol. Chem. 254:10700-10706 (1979)).

Bacterial cells can also induce host cells to produce chemotactic factors, e.g., by activating components of the host's complement system, giving rise to the local production of the chemotactic molecules, C5a and C5b67. Once an immune response ensues in the host, IgG antibody molecules may also act as chemotactic factors, as can molecules produced by activated T lymphocytes. Different chemotactic molecules have selectivity for various PMNs (e.g. neutrophils, basophils, eosinophils), mast cells, monocytes/macrophages, or lymphocytes, based on the presence of the appropriate receptors on the inflammatory cell type.

The identification and characterization of the sites of infection and inflammation are important for clinical diagnosis in human and veterinary medicine. In the case of early localized infections, it is frequently necessary to search for "hidden sites of inflammation" in individuals who present with clinical syndromes no more specific than fever and weight loss. Similarly, in patients with autoimmune diseases such as rheumatoid arthritis or in recipients rejecting tissue or organ allografts, the capacity to identify inflammatory sites, define their extent, and monitor changes following initiation of therapy is important for effective clinical area.

Not surprisingly, then, much effort has been expended and many techniques developed in an attempt to identify the site(s) and assess the extent of the inflammatory process. These techniques include conventional x-ray techniques, computerized axial tomographic scanning (CAT scanning), and a variety of radionuclide scans. (Sutton, A Textbook of Radiology and Imaging, 3rd Ed.,

Churchill Livingston, 1980; Clinical Nuclear Medicine, Maysey et al., ed., W.B. Sanders, 1983.) Examples of techniques for radionuclide scans which have been utilized include:

1. ^{67}Gallium, which binds to the plasma protein, transferrin, after injection and tends to localize at sites of chronic inflammation;
2. ^{111}Indium labeled granulocytes, which, when reinjected into the host, will accumulate at the site of inflammation;
3. Radiolabeled chelates, which pass into the extracellular fluid and can then accumulate at sites of fluid accumulation; and
4. Thallium scan or so-called first pass radionuclide angiogram to assess areas of increased blood flow.

Thakur, M.L., et al., have extensively analyzed and discussed methods based on neutrophil labeling in vitro (Sem. Nucl. Med. 14:107-117) (1984)). In this approach, an individual's neutrophils are labeled with a gamma emitting radionuclide, ^{111}In being the nuclide of choice. Such labeled neutrophils could be used in in vivo kinetic studies and for imaging of inflammatory foci. One disadvantage of this technique is the need to remove and isolate neutrophils prior to their labeling in vitro.

Zoghbi, S.S. et al., (J. Nuc. Med. 22:p32) (1981)), who labeled the chemotactic peptide f_Met-Leu-Phe with ^{111}In using the protein transferrin coupled to the peptide and suggested that this reagent had promise for selectively labeling human neutrophils. While this approach provides a potential solution for the problem of specificity of labeling, it does not suggest a solution for the complication of removing cells from an individual, manipulating them in vitro, and then reinfusing them.

One report describes an attempt to localize sterile abscesses in vivo by direct injection of ^{125}I-labeled N-Formyl-Nle-Leu-Phe-Nle-Tyr-Lys into rabbits (Jiang, M.-S. et al., Nucl.-Med. 21:110-113 (1982)). While achieving effective laboling ratios (abscess-to-muscle), use of this agent caused transient neutropenia followed by

rebound neutrophilia. The authors recognized that further development was needed to avoid the side effects of neutropenia/neutrophilia and make this method clinically useful.

Whereas the above techniques may provide useful information, they result in an unacceptably high frequency of both false positive and false negative results, require an unacceptable amount of handling and processing, or are accompanied by unacceptable side effects. Thus, there is a recognized need in the art for more direct, more sensitive and more specific methods for detecting and localizing sites of infection or inflammation, particularly techniques that could be performed serially to assess the response to therapy over time.

SUMMARY OF THE INVENTION

The present invention relates to a substantially non-invasive method for imaging sites of infection or inflammation.

The inventors have discovered that detectably labeled chemotactic peptides injected systematically into animals accumulate at sites of local infection.

The present invention thus relates to an *in vivo* method of detecting a site or sites of infection or inflammation in an individual. This method comprises administering to the individual a detectably labeled chemotactic peptide wherein the peptide substantially accumulates at the site of infection or inflammation, but does not accumulate at uninfected, non-inflamed sites. The invention also includes the various chemotactic peptides to which appropriate chelating molecules and detectable labels have been conjugated.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a graph demonstrating the results of an assay of the binding of four chemotactic peptides, conjugated with DTPA, to human neutrophils. The assay is a competitive binding assay in

which [^{3}H]for-MLF is displaced by increasing concentrations on unlabeled peptide.

Figure 2 is a graph demonstrating the results of an assay of four chemotactic peptides, conjugated to DTPA, for stimulation of superoxide production by human neutrophils. MLF was included in the assay for comparison.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The terms "inflammation" or "site of inflammation" are used to denote conditions and their locations which occur in an individual due to tissue damage, regardless of the underlying cause or etiology. This tissue damage can result from microbial invasion, auto-immune processes, tissue or organ allograft rejection, or such injurious external influences as heat, cold, radiant energy, electrical or chemical stimuli, or mechanical trauma. Whatever the cause or bodily site, the ensuing inflammatory response is quite similar, consisting of a complicated set of functional and cellular adjustments, involving the changes in microcirculation, movement of fluids, and influx and activation of inflammatory cells (leukocytes).

The term "infection" denotes invasion by bacteria, viruses, fungi, protozoa, and other microorganisms.

The term "individual" is meant to include both animals and humans.

In detecting an in vivo site of infection or inflammation in an individual, the detectably labeled chemotactic peptide is advantageously given in a dose which is diagnostically effective. The term "diagnostically effective" means that the amount of detectably labeled chemotactic peptide administered is sufficient to enable detection of the site of infection or inflammation when compared to the background signal.

Generally, the dosage of detectably labeled chemotactic peptide for diagnosis will vary depending on considerations such as age, condition, sex, and extent of disease in the patient, counterindications, if any, and other variables, to be adjusted by

the individual physician. Dosage can vary from 0.01 µg/kg to 2,000 µg/kg, preferably 0.1 µg/kg to 1,000 µg/kg.

The term "chemotactic peptide" as used in this invention is meant to include but is not limited to molecules having the following general structure:

M - X - Y - Leu - Phe - Z - W

Where: X = Formyl for agonists
- A more bulky group such as t - Boc for antagonist.

Y = Met or Nle.

Z* = is a spacer sequence such as Gly - Gly - Gly

W* = is a labeling or attachment substituent, i.e.,
N.epsilon (DTPA) Lys - putrsine for labeling.
- OSU (SO_3) for attachment to a high molecular weight carrier

*At the Z and W positions either D or L amino acids can be used.

Examples of suitable compounds include, but are not limited to:

For-Nle-Leu-Phe-Nle-Tyr-Lys - DTPA
For-Met-Leu-Phe-Pu - DTPA
For-Nle-Leu-Phe-Lys - DTPA
For-Nle-Leu-Phe-Lys(NH_2) - DTPA
For-Met-Leu-Phe - Lys - DTPA
For-Met-Leu-Phe - D-Lys (NH_2) - DTPA
Ac-Nle-Leu-Phe-Lys(NH_2) - DTPA

The term "diagnostically labeled" means that the chemotactic peptide has attached to it a diagnostically detectable label.

There are many different labels and methods of labeling known to those of ordinary skill in the art. Examples of the types of labels which can be used in the present invention include radioactive isotopes, paramagnetic isotopes, and compounds which can be imaged by positron emission tomography (PET). Those of ordinary skill in the art will know of other suitable labels for binding to the chemotactic peptides used in the invention, or will be able to ascertain such, using routing experiments. Furthermore, the binding of these labels to the chemotactic peptide can be done using standard techniques common to those of ordinary skill in the art.

For diagnostic *in vivo* imaging, the type of detection instrument available is a major factor in selecting a given radionuclide. The radionuclide chosen must have a type of decay which is detectable by a given type of instrument. In general, any conventional method for visualizing diagnostic imaging can be utilized in accordance with this invention.

Another important factor in selecting a radionuclide in *in vivo* diagnosis is that the half-life of a radionuclide be long enough so that it is still detectable at the time of maximum uptake by the target issue, but short enough so that deleterious radiation of the host is minimized. In one preferred embodiment, a radionuclide used for *in vivo* imaging does not emit particles, but produces a large number of photons in a 140-200 keV range, which may be readily detected by conventional gamma cameras.

For *in vivo* diagnosis, radionuclides may be bound to chemotactic peptide either directly or indirectly by using an intermediary functional group. Intermediary functional groups which are often used to bind radioisotopes which exist as metallic ions to chemotactic peptides are the chelating agents, diethylene triamine pentaacetic acid (DTPA) and ethylene diamine tetracetic acid (EDTA). Examples of metallic ions which can be bound to chemotactic peptides are ^{99m}Tc, ^{123}I, ^{111}In, ^{131}I, ^{97}Ru, ^{67}Cu, ^{67}Ga, ^{125}I, ^{68}Ga, ^{72}As, ^{89}Zr, and ^{201}Tl.

In addition to identifying and characterizing sites of local infection and inflammation, the method of the invention can be used to monitor the course of inflammation in an individual. Thus, by measuring the increase or decrease in the size or number of inflammatory sites it is possible to determine whether a particular therapeutic regimen aimed at ameliorating an infection or other cause of the inflammatory process, or directed to the inflammatory process itself, is effective.

In another embodiment the invention is used for diagnosing the specific underlying cause of the inflammation at the site. In this method an individual suspected of having an inflammatory site is first administered a diagnostically effective amount of chemotactic

peptide, as previously described, and is then imaged to determine the presence and location of said site.

In another embodiment, the chemotactic peptides of this invention are "therapeutically conjugated" and used to deliver the therapeutic agent to the site of infection or inflammation. The term "therapeutically conjugated" means that the chemotactic peptide is conjugated to a therapeutic agent. The therapeutic agents used in this manner act are directed either to the underlying cause of the inflammation, such as for example, the infectious organisms or a tumor, or to components of the inflammatory process themselves. Examples of agents used to treat inflammation are the steroidal and non-steroidal anti-inflammatory drugs. Many of the non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis.

Other therapeutic agents which can be coupled to the chemotactic peptides according to the method of the invention are drugs, radioisotopes, lectins, toxins, and antimicrobial agents. The therapeutic dosage administered is an amount which is therapeutically effective, and will be known to one of skill in the art. The dose is also dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired, such as, for example, anti-inflammatory effects or anti-bacterial effect.

Lectins are proteins, often derived from plants, that bind to carbohydrates. Many lectins are also able to agglutinate cells and several stimulate lymphocytes. Ricin is a toxic lectin which has been used therapeutically by binding the alpha-chain, which is responsible for toxicity, to an antibody molecule to enable site-specific delivery of the toxic effect. In an embodiment of this invention, ricin alpha-chain is conjugated to a chemotactic peptide.

Toxins are poisonous substances produced by plants, animals, and microorganisms that, in sufficient dose, can be lethal. Diphtheria toxin, a protein produced by Corynebacterium diphtheriae, consists of separable alpha and beta subunits. The toxic component can be bound to a chemotactic peptide and used for site-specific delivery to the site of an infection or inflammatory response.

Examples of radioisotopes which can be bound to the chemotactic peptide for therapeutic purposes, used according to the method of the invention, are ^{125}I, ^{131}I, ^{90}Y, ^{67}Cu, ^{217}Bi, ^{211}At, ^{212}Pb, ^{47}Sc, and ^{109}Pd.

Anti-microbials are substances which inhibit such infectious microorganisms as bacteria, viruses, fungi, and parasites (Goodman, A.G., et al., 1985, supra), and can be any of those known to individuals of ordinary skill in the art.

Other therapeutic agents which can be coupled to the chemotactic peptides or specific antibodies used according to the method of the invention are known, or can be easily ascertained, by those of ordinary skill in the art.

Preparations of the imaging chemotactic peptides or therapeutically-conjugated chemotactic peptides for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propyleneglycol, polyethyleneglycol, vegetable oil such as olive oil, and injectable organic esters such as ethyloleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media, parenteral vehicles including sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present, such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like. See, generally, Remington's Pharmaceutical Science, 16th ed., Mac Eds, 1980.

Preparations of the imaging chemotactic peptides or therapeutically-conjugated chemotactic peptides of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, including subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. A preferred route of administration of the detectably labeled chemotactic peptides for

imaging is the intravenous route. The chemotactic peptide can be administered in a single bolus, or by gradual perfusion, which is preferably intravenous and uses peristaltic means to accomplish the gradual perfusion.

This invention can be utilized to detect infection or inflammation at a wide variety of body sites including, but not limited to, muscle, vascular walls, abdomen, pelvis, bone, joint or lung.

This invention is utilized to diagnose infection by any of a number of microorganisms, or inflammation caused by such infection, or by trauma, autoimmune processes or tumors.

The invention is also useful as a means to evaluate the efficacy of, and responses to, therapeutic treatment of infection or inflammation.

The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific examples which are provided herein for purposes of illustration only, and are not intended to be limiting unless otherwise specified.

EXAMPLE 1

IMAGING OF FOCAL SITES OF EXPERIMENTAL BACTERIAL INFECTION

The chemotactic peptide N-formyl-Nle-Leu-Phe-Nle-Tyr-Lys was synthesized using standard solid phase methods well-known in the art. The epsilon amino group of the C-terminal lysine was modified with DTPA using a cyclic anhydride. The EC_{50} of the nascent peptide and the DTPA derivative were nearly identical, approximately 10^{-9} M. (Similar results were obtained with all peptides tested). This indicated that the derivatization with DTPA did not affect the biological activity of the peptide. This result was very surprising, since one would expect that introducing the highly negatively charged DTPA group would markedly alter the properties of such small peptides. The peptide was readily radiolabeled with ^{111}In.

Six Sprague-Dawley rats were experimentally infected by the injection of 10^8 viable E. coli into their left thighs. Approximately 100 μCi of the labeled peptide (5-10 μg) was injected 24 hours after infection. Serial gamma camera images revealed localization of radioactivity at the site of infection with peak accumulation occurring at 1 hour (target-to-background ration was about 4.0). By 2 hours, the level of activity had decreased in intensity and by 24 hours, the lesion was barely discernible.

These results establish the utility of this new agent for imaging focal sites of inflammation in an animal mode of infection.

EXAMPLE 2
BIODISTRIBUTION OF LEUKOCYTE BINDING AND BIOACTIVITY OF CHEMOTACTIC PEPTIDES

Leukocytic Binding: Four chemotactic peptides conjugated with DTPA were assayed for binding to human neutrophils by a competitive binding assay in which [^{3}H]for-MLF was displaced by increasing concentrations of unlabeled peptide (Babior, B.M. et al., J. Clin. Invest. 52:741 (1973)). The results are shown in Figure 1. Three non-DTPA derivatized peptides were included in the assay for comparison.

SOO Production: Four chemotactic peptides conjugated with DTPA were assayed for stimulation of superoxide production by human neutrophils (Pike, M.C. et al., Methods in Enzymol. 162:236 (1988)). These results are shown in Figure 2. MLF was included in the assay for comparison purposes.

In Vivo Neutropenia: Two chemotactic peptides conjugated with DTPA were administered to rats at a dose approximately 10-fold higher than the standard imaging dose. Peripheral blood was collected (via tail vein) at 5 min pre-injection and at 1, 2, 5, 10, 15 and 30 minutes post-injection. In all animals studied, there was no significant induction of neutropenia.

Having now fully described this invention, it will be appreciated by those skilled in the art that the same can be

performed within a wide range of equivalent parameters, concentrations, and conditions without departing from the spirit and scope of the invention and without undue experimentation.

While this invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications. This application is intended to cover any variations, uses, or adaptations of the inventions following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice to the essential features hereinbefore set forth as follows in the scope of the appended claims.

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WHAT IS CLAIMED IS:

1. A method of detecting a site of infection or inflammation in an individual which comprises:

a. administering to said individual a diagnostically effective amount of detectably labeled chemotactic peptide

N - X - Y - Leu - Phe - Z - W

Where: X = Formyl for agonists
- A more bulky group such as t - Boc for antagonist.

Y = Met or Nle.

Z*= is a spacer sequence such as Gly - Gly - Gly

W*= is a labeling or attachment substituent, i.e., N.epsilon (DTPA) Lys - putrsine for labeling.
- OSU (SO_3) for attachment to a high molecular weight carrier

*At the Z and W positions either D or L amino acids can be used.

which substantially accumulates at said site which is infected or inflamed and does not substantially accumulated at said site which is not infected or inflamed, and

b. detecting said chemotactic peptide.

2. The method of claim 1 wherein said chemotactic peptide is conjugated to DTPA.

3. The method of claims 1 or 2, wherein said detectable label is a radioactive isotope.

4. The method of claim 1 wherein said chemotactic peptide is N-formyl-Nle-Leu-Phe-Gly-Gly-Gly-O-Succinyl-SO_3

5. The method of claim 1, wherein said administration is parenteral.

6. The method of claim 5, wherein said parenteral administration is by intradermal, subcutaneous, intramuscular, intraperitoneal, or intravenous injection.

7. The method of claim 1, wherein said administration is by gradual perfusion.

8. The method of claim 7, wherein said gradual perfusion is by the intravenous route using peristaltic means.

9. The method of any one of claims 1-8, wherein said individual is a human.

10. A chemotactic peptide selected from the group consisting of
For-Nle-Leu-Phe-Nle-Tyr-Lys - DTPA
For-Met-Leu-Phe-Pu - DTPA
For-Nle-Leu-Phe-Lys - DTPA
For-Nle-Leu-Phe-Lys(NH_2) - DTPA
For-Met-Leu-Phe - Lys - DTPA
For-Met-Leu-Phe - D-Lys (NH_2) - DTPA
Ac-Nle-Leu-Phe-Lys(NH_2) - DTPA
diagnostically conjugated to a detectable label, capable of accumulating at a site of infection or inflammation in an individual, wherein said chemotactic peptide shows substantially no accumulation in said site in the absence of infection or inflammation.

11. The chemotactic peptide of claim 10 conjugated to DTPA.

12. The chemotactic peptide of claim 10 or 11, wherein said detectable label is a radioactive isotope.

13. The chemotactic peptide of claim 10 which is N-formyl-Nle-Leu-Phe-Gly-Gly-Gly-O-Succinyl-SO_3

14. A method for treating a localized site of infection or inflammation in an individual which comprises administering to said individual a therapeutically effective amount of a therapeutically-conjugated chemotactic peptide having the general formula:

N - X - Y - Leu - Phe - Z - W

Where: X = Formyl for agonists
- A more bulky group such as t - Boc for antagonist.

Y = Met or Nle.

Z* = is a spacer sequence such as Gly - Gly - Gly

W* = is a labeling or attachment substituent, i.e., N^{ϵ}-epsilon (DTPA) Lys - putrsine for labeling.
- OSU (SO_3) for attachment to a high molecular weight carrier

*At the Z and W positions either D or L amino acids can be used.

which substantially accumulates at said site which is infected or inflamed and does not substantially accumulated at said site which is not infected or inflamed.

FIGURE 1

RECEPTOR BINDING OF CHEMOTACTIC PEPTIDES

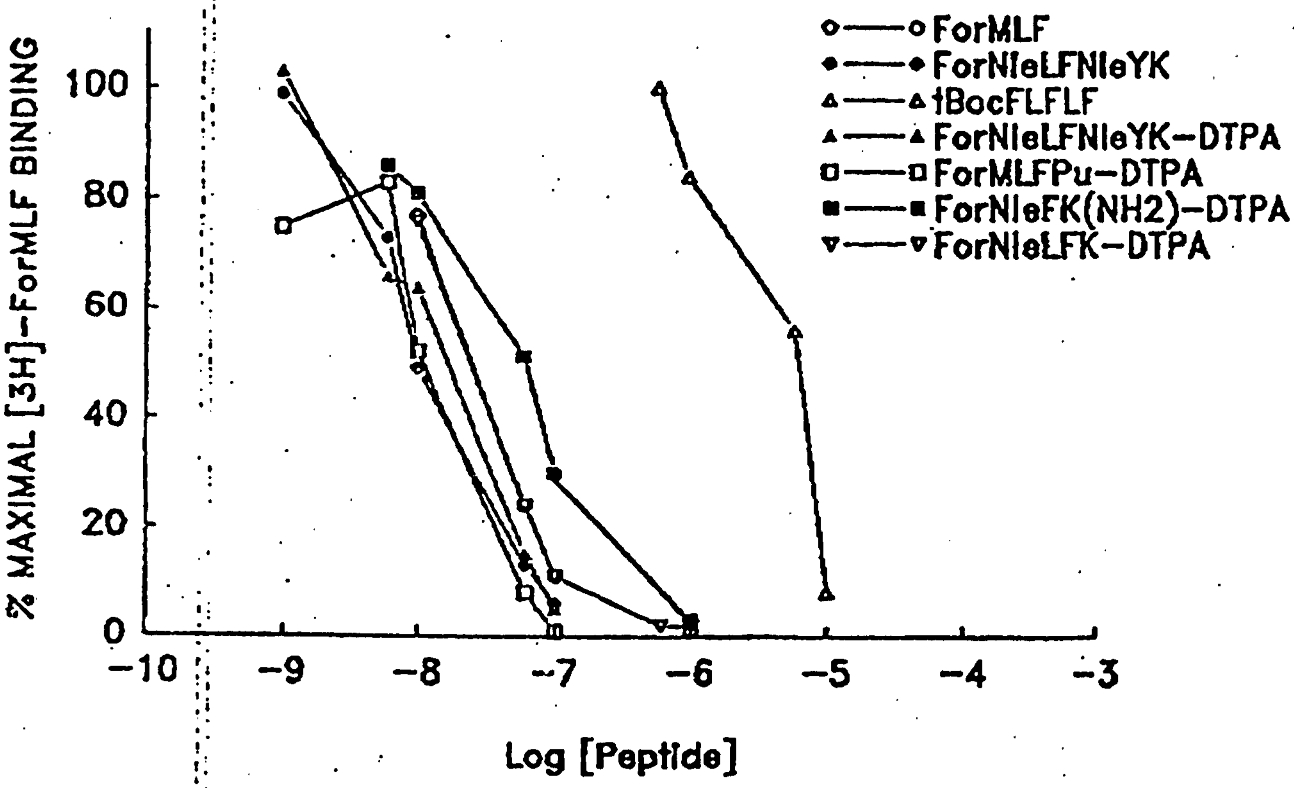

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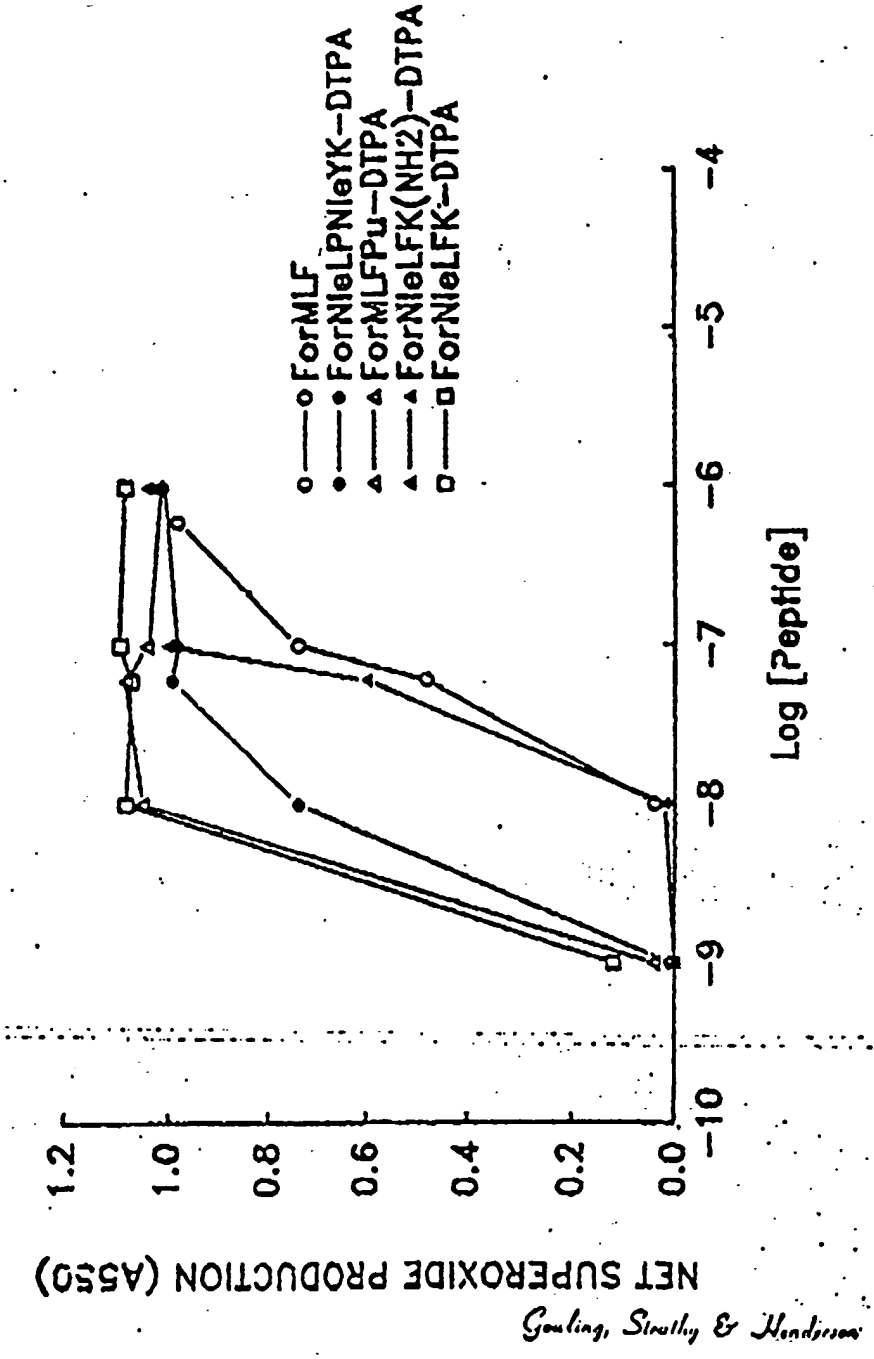
FIGURE 2

SUPER OXIDE PRODUCTION BY LEUKOCYTES



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